Remarks

Applicant appreciates the thorough examination of the present application as evidenced by the final Office Action mailed April 3, 2003 (the "Final Action").

Claims 22-29 and 31-53 are pending in the present application. Claims 25-29, 33-36, 38-43, 45-48 and 50 have been withdrawn from consideration. Applicants have canceled claims 25-29, 33-36, 38-43, 45-48 and 50. Claims 22-24, 31-32, 37, 44, 49 and 51-53 stand rejected.

I. Interview Summary

Applicant and the Applicant's representatives, Kenneth D. Sibley and Shawna Cannon Lemon, appreciated the opportunity to speak with the Examiner on June 6, 2003. During this telephonic interview, the Examiner was introduced to the inventor, Dr. Richard C. Boucher, Jr. As the Examiner may recall, Dr. Boucher is currently a Professor of Medicine and the Director of the Cystic Fibrosis/Pulmonary Research and Treatment Center at the University of North Carolina at Chapel Hill School of Medicine, where he holds an endowed chair as a William Rand Kenan Professor.

During the telephonic interview, the Examiner requested information regarding the protocol for diagnosis of cystic fibrosis as it relates to U.S. Patent No. 5,817,028 to Anderson. The Examiner further requested data showing an increase in drug penetration associated with the methods of the present invention. Applicant hereby provides the following response to address the Examiner's concerns regarding the above-referenced case.

II. Rejection Under 35 U.S.C. § 103

Claims 22-24, 31-32, 37, 44, 49 and 51-55 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,817,028 to Anderson (Anderson), in view of U.S. Patent No. 5,876,700 to Boucher, Jr. et al. (Boucher, Jr. et al.) and U.S. Patent No. 5,837,266 to Jungherr et al. (Jungherr et al.). More specifically, at page 3, the Office Action mailed July 16, 2002 (Paper Number 13) states that "it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to treat a subject with cystic fibrosis by administering to the subject a combination of osmolyte, such as potassium sulfate and a sodium channel blocker, such as benzamil or phenamil." Applicant respectfully traverses this rejection.

A. Anderson is not directed to treatment of chronic bstructive pulmonary disorders

Anderson proposes the following:

> "[A] method for attempting to provoke airway narrowing in a subject comprising the steps of (a) causing the subject to inhale into the airways an effective amount of a substance capable of altering the osmolarity of airway surface liquid in the subject, which substance is in the form of a dispersible dry powder containing an effective proportion of particles of a respirable size, and (b) measuring in the subject a parameter indicative of the resistance to air flow of the subject's airways."

Col. 2, lines 35-44.

As noted by the Applicant during the June teleconference, Anderson proposes a method and device for the provocation of air passage narrowing and/or the induction of sputum. Contrary to the assertions of the Examiner, Anderson does not propose the **treatment** of chronic obstructive pulmonary disease. More specifically, Anderson presents a method "for testing the susceptibility of a person to asthma." *See* Abstract. The Anderson method enables the detection of airway narrowing which is indicative of a propensity for asthma. *See* Abstract. Clearly, a method of inducing airway narrowing would not be desirable for **treating** a chronic obstructive pulmonary disease such as cystic fibrosis.

The Examiner relies upon the background section of Anderson for the proposition that Anderson is directed to treatment of cystic fibrosis. Applicant notes that this reference does not refer to **treatment** of cystic fibrosis. Instead, this language refers to the **diagnosis** of these respiratory disorders, and more specifically, use of this technique as a research tool. The mucociliary clearance as cited in Anderson relates to short-term mucociliary clearance for sputum induction for diagnostic purposes. A copy of an article by Aitken et al. *Chest* 123(3): 792-799 (2003) and a copy of an article by Henig et al. *Thorax* 56:306-311 (2001) is attached herewith. These article show that one of ordinary skill in the art would recognize that the technique cited in the background section of Anderson is directed to diagnosis and not treatment of asthma.

Consequently, Anderson does not teach or suggest compounds and methods for the treatment of airway diseases and for the delivery of airway drugs as disclosed in the present application. Moreover, a person of ordinary skill in the art to which the present invention pertains would not be motivated to combine Anderson (directed to methods and devices for

the provocation of airway passage narrowing and/or induction of sputum for diagnostic testing) with Boucher, Jr. et al. (directed to methods of hydrating lung mucous secretions).

Applicant further submits that Jungherr et al. does not supply the missing recitations or motivation to combine these references in order to arrive at the present invention. Instead, Jungherr et al. proposes "[a] sustained release drug delivery composition and a method of making same . . . which comprises microspheres containing a pharmaceutically active agent, a core of a ion-exchange resin and a polymeric coating completely surrounding the core wherein the coating is water-insoluble and hydrolytically stable in physiological environments." *See* Abstract. Thus, Jungherr et al. does not provide motivation for one of ordinary skill in the art to combine the cited references where one of ordinary skill in the art clearly would not rely on the teachings of Jungherr et al. in pursuit of the present invention.

Accordingly, Applicant submits that claims 22-24, 31-32, 37, 44, 49 and 51-53 are not obvious in view of Anderson, Boucher, Jr. et al. and/or Jungherr et al. and respectfully requests that this rejection be withdrawn.

B. The methods of the present invention show enhanced drug penetration through thickened mucus

In response to the Examiner's request for additional data to show an increase in drug penetration associated with the methods of the present invention, Applicant provides Figures 1 and 2 in the exhibit attached hereto.

Figure 1 illustrates studies wherein well-differentiated cystic fibrosis bronchial epithelia were loaded with 5 uM Snarf (Molecular Probes, USA) to denote the cell cytosol, red in color (Panel A). Isotonic solution (1.5 uL) was added to the apical surface of a thickened mucus layer followed by fluorescein 20 uM (green in color, Panel B). Panel B image was captured 5 min post fluorescein addition. Applicants note that the drug surrogate was trapped in thickened mucus and access to epithelial surface (and epithelial uptake) was restricted. No cellular uptake was detectable. Applicant further notes that fluorescein was employed in this assay for the molecular weight similarity to that of amiloride (332 compared to 266, respectively,) and assists in the visualization of mucus viscosity and its significance in drug transport.

Figure 2 illustrates the same method as applied in Figure 1, except a hypertonic solution (~300 mM potassium phosphate) was added to the apical surface rather than isotonic

saline. Hypertonic solution swelled the mucus, allowing the drug surrogate (fluorescein) to penetrate to the cell surface, following which there was rapid cellular uptake of the surrogate.

Thus, the present invention provides enhanced drug penetration through the thickened mucus to the cell surface.

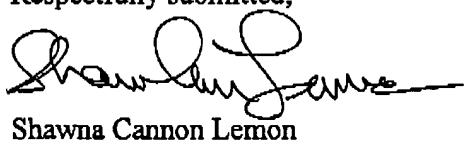
Accordingly, Applicant submits that claims 22-24, 31-32, 37, 44, 49 and 51-53 are not obvious in view of Anderson, Boucher, Jr. et al. and/or Jungherr et al. and respectfully requests that this rejection be withdrawn.

III. Conclusion

In view of the foregoing amendments and remarks that address the Examiner's concerns as expressed during the June 6, 2003 teleconference and the final Office Action, Applicant respectfully requests that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. Any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

No fee is believed due. However, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 50-0220.

Respectfully submitted,



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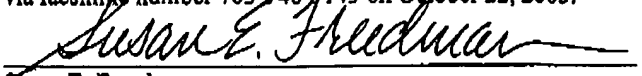

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Date of Signature: October 22, 2003